

# AZD1480: A Phase I Study of a Novel JAK2 Inhibitor in Solid Tumors

ELIZABETH R. PLIMACK,<sup>a</sup> PATRICIA M. LORUSSO,<sup>b</sup> PATRICIA MCCOON,<sup>c</sup> WEIFENG TANG,<sup>c</sup> ANNETTA D. KREBS,<sup>c</sup> GREGORY CURT,<sup>c</sup> S. GAIL ECKHARDT<sup>d</sup>

<sup>a</sup>Fox Chase Cancer Center, Temple Health, Philadelphia, Pennsylvania, USA; <sup>b</sup>Karmanos Cancer Institute, Detroit, Michigan, USA; <sup>c</sup>AstraZeneca, Wilmington, Delaware, USA; <sup>d</sup>University of Colorado Cancer Center, Aurora, Colorado, USA

Disclosures of potential conflicts of interest may be found at the end of this article.

To access the full Clinical Trial Report, including disclosures, see: <http://clinicaltrialresults.theoncologist.com/search/results>

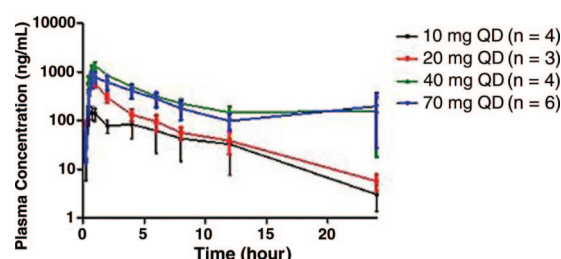
## AUTHOR SUMMARY

### ABSTRACT

**Background:** AZD1480 is a novel agent that inhibits Janus-associated kinases 1 and 2 (JAK1 and JAK2). The primary objective of this phase I study was to investigate the safety and tolerability of AZD1480 when administered as monotherapy to patients with solid tumors.

**Methods:** Thirty-eight patients with advanced malignancies were treated at doses of 10–70 mg once daily (QD) and 20–45 mg b.i.d. .

**Results:** Pharmacokinetic (PK) analysis revealed rapid absorption and elimination with minimal accumulation after repeated QD or b.i.d. dosing. Exposure increased in a dose-dependent manner from 10–50 mg. Maximum plasma concentration ( $C_{max}$ ) was attained ~1 hour after dose, and  $t_{1/2}$  was ~5 hours. Pharmacodynamic analysis of circulating granulocytes demonstrated maximum phosphorylated STAT3 (pSTAT3) inhibition 1–2 hours after dose, coincident with  $C_{max}$ , and greater pSTAT3 inhibition at higher doses. The average pSTAT3 inhibition in granulocytes at the highest dose tested, 70 mg QD, was 56% (standard deviation:  $\pm 21\%$ ) at steady-state drug levels. Dose-limiting toxicities (DLTs) consisted of pleiotropic neurologic adverse events (AEs), including dizziness, anxiety, ataxia, memory loss, hal-



**Figure 1.** Plasma concentration (mean  $\pm$  SD) of AZD1480 versus time profile on day 1.

lucinations, and behavior changes. These AEs were generally reversible with dose reduction or treatment cessation.

**Conclusions:** Whether the DLTs were due to inhibition of JAK-1/2 or to off-target effects is unknown. The unusual DLTs and the lack of clinical activity led to discontinuation of development. *The Oncologist* 2013;18:819–820

## DISCUSSION

Constitutive activity of the JAK/STAT signaling pathway has been implicated in a wide variety of solid tumors, including

**Table 1.** Dose escalation and dose limiting toxicities

Dose level	Dose of drug	Number enrolled	Number evaluable for toxicity	Number with a dose limiting toxicity	Dose limiting toxicity information
1	10 mg QD	4	3	0	
2	20 mg QD	3	3	0	
3	40 mg QD	4	4	0	
4	70 mg QD	6	6	0	
5	20 mg BID	6	5	1	Ataxia/grade 2
6	30 mg BID	7	5	1	Dizziness/grade 3
7	35 mg BID	5	3	2	Hallucination/grade 2 Anxiety/grade 3
8	45 mg BID	3	2	0	

ClinicalTrials.gov Identifier: NCT01112397  
Sponsor(s): AstraZeneca

Principal Investigator: Elizabeth R. Plimack  
IRB Approved: Yes

Correspondence: Elizabeth Plimack, M.D., Fox Chase Cancer Center, Temple Health, 333 Cottman Avenue, Philadelphia, Pennsylvania 19111, USA. Telephone: 215-728-3889; Fax: 215-728-3639; E-Mail: [elizabeth.plimack@fccc.edu](mailto:elizabeth.plimack@fccc.edu) Received April 26, 2013; accepted for publication June 3, 2013; first published online in *The Oncologist Express* on July 11, 2013. ©AlphaMedPress; the data published online to support this summary is the property of the authors. <http://dx.doi.org/10.1634/theoncologist.2013-0198>

prostate, head and neck, glioblastoma, colorectal, and ovarian cancers [1–6]. AZD1480 is a novel JAK1/JAK2 inhibitor that has been shown to suppress growth of solid tumor xenografts [7]. In this phase I study, AZD1480 was administered as an oral QD or b.i.d. monotherapy to patients with advanced solid tumors at eight dose levels in the ranges of 10–70 mg QD and 20–45 mg b.i.d. using a standard 3 + 3 design. AZD1480 had fast absorption, fast elimination, and dose-dependent increase in exposure from 10 mg to 50 mg. One patient, treated at 30 mg b.i.d., submitted pre- and post-treatment tumor biopsies, analysis of which showed a 50% reduction in pSTAT3, indicating pharmacodynamic effect. There were no Response Evaluation Criteria in Solid Tumors responses. One patient with lung cancer had stable disease for >4 months (145 days). No DLTs were noted at any of the QD doses. Based on PK analysis, b.i.d. dosing cohorts were subsequently opened. DLTs were noted at three of the four b.i.d. dose levels. All DLTs were neuropsychiatric in nature (dizziness, ataxia, hallucinations, and anxiety) and were reversible in all cases but one, a case of grade 3 anxiety. Inclusive of the DLTs, neuropsychiatric AEs of any grade were reported by 53% of patients in the b.i.d. dosing

cohorts, with dizziness and ataxia being the most common. The mechanism of this unusual toxicity profile is unclear. One hypothesis is that off-target inhibition of TRKB caused the wide range of neuropsychiatric effects observed in this trial, based on data showing that AZD1480 is equipotent against the TRK family (TRKA, TRKB, TRKC). TRKB is a receptor tyrosine kinase with signaling activated by neurotrophins [8]. Anxious behavior has been demonstrated in mice with inactivated TRKB [9]. An alternate hypothesis is that the central nervous system penetration of AZD1480 affected JAK signaling in the brain. In rats, AZD1480 had good blood-brain barrier penetration with a brain-to-blood ratio of 0.5. At this time, there are insufficient data to differentiate between these hypotheses. Unfortunately, this unusual toxicity profile and overall lack of clinical activity led to discontinuation of development of AZD1480. JAK2 targeting remains an area of active investigation for solid tumors.

## DISCLOSURES

Author disclosures available online.

## REFERENCES

1. Levy DE, Inghirami G. Stat3: A multifaceted oncogene. *Proc Natl Acad Sci USA* 2006;103:10151–10152.
2. Dhir R, Ni Z, Lou W et al. Stat3 activation in prostatic carcinomas. *Prostate* 2002;51:241–246.
3. Grandis JR, Drenning SD, Zeng Q et al. Constitutive activation of Stat3 signaling abrogates apoptosis in squamous cell carcinogenesis in vivo. *Proc Natl Acad Sci USA* 2000;97:4227–4232.
4. Silver DL, Naora H, Liu J et al. Activated signal transducer and activator of transcription (STAT) 3: Localization in focal adhesions and function in ovarian cancer cell motility. *Cancer Res* 2004;64:3550–3558.
5. Grivennikov S, Karin E, Terzic J et al. IL-6 and Stat3 are required for survival of intestinal epithelial cells and development of colitis-associated cancer. *Cancer Cell* 2009;15:103–113.
6. Inda MM, Bonavia R, Mukasa A et al. Tumor heterogeneity is an active process maintained by a mutant EGFR-induced cytokine circuit in glioblastoma. *Genes Dev* 2010;24:1731–1745.
7. Hedvat M, Huszar D, Herrmann A et al. The JAK2 inhibitor AZD1480 potently blocks Stat3 signaling and oncogenesis in solid tumors. *Cancer Cell* 2009;16:487–497.
8. Skaper SD. The neurotrophin family of neurotrophic factors: An overview. *Methods Mol Biol* 2012;846:1–12.
9. Bergami M, Rimondini R, Santi S et al. Deletion of TrkB in adult progenitors alters newborn neuron integration into hippocampal circuits and increases anxiety-like behavior. *Proc Natl Acad Sci USA* 2008;105:15570–15575.